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doi:10.1016/j.jacc.2008.10.059

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**Reply**

We thank Dr. Opie for his comment on our recent publication (1). Caloric restriction is a powerful tool to reverse at least some of the negative effects induced by obesity in diabetic patients.

The hypothesis that the effects of the metabolic syndrome arise from high levels of circulating fatty acids and cytokines derived from (visceral) adipose tissue (2) is indeed supported by our data, although one has to use caution in considering this a causal relationship, solely based on the present results.

On the other hand, it was recently shown, in another group of patients with type 2 diabetes, that plasma free fatty acids are, at least to some extent, involved in the effects of short-term caloric restriction on the heart (3). We showed that short-term caloric restriction induced increased levels of free fatty acids and consequently, myocardial triglycerides accumulated. This was associated with a change in diastolic function. Interestingly, when this caloric restriction was combined with administration of the antilipolytic drug acipimox, these changes were not observed. These results provide circumstantial evidence for the relevance of fatty acids in myocardial triglyceride accumulation and changes in diastolic function in this particular group of patients, perfectly in line with the hypothesis stating the relevance of fatty acids and cytokines released by adipose tissue.

We therefore generally agree with Dr. Opie that our results are exciting, and they underline the high potential of treatments aiming to decrease adipose tissue compartments to reverse the effects of metabolic disease on the heart, whether associated with fatty acids released from adipose tissue or not.

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doi:10.1016/j.jacc.2008.11.043

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## Multiple Mechanisms Affect the Clopidogrel Response

We read with interest the paper by Ang et al. (1) in a previous issue of the *Journal*. The purpose of the study was to identify factors associated with lower platelet inhibition (PI) with clopidogrel in patients with cardiovascular disease. Their results showed that elevated plasma fibrinogen  $\geq 375$  mg/dl is a unique factor associated with lower PI in diabetic patients, whereas increased body mass index remains independently associated with lower PI after clopidogrel therapy. They also identify the presence of diabetes mellitus as a factor associated with lower PI. However, this finding was only significant in the presence of an elevated serum fibrinogen level. No other statistical association with PI was found in the multiple variable model.

Although these findings are interesting, other factors involving clopidogrel response have not been completely evaluated. For example, the impact of genetic polymorphisms or other genetic factors on clopidogrel response has not been evaluated in the study. It is well known that P2Y<sub>12</sub> receptor inhibition is implemented by an active metabolite of clopidogrel. Therefore, genetic variants of enzymes within the metabolic pathways (P450 enzymes) or downstream targets of the active metabolite (P2Y, platelet glycoproteins IIb/IIIa and Ia) might affect clopidogrel response. Moreover, the metabolic activity of the P450 enzymes varies considerably among individuals. Genetic polymorphisms of the cytochrome P450 isoenzymes such as CYP3A4\*1B (rs2740574), CYP3A5\*3 (rs776746), and CYP2C19\*2 (rs4244285) have been implicated to modulated individual response to clopidogrel (2). However, only CYP2C19\*2 (SNP rs4244285, AA